CADTH

CADTH COMMON DRUG REVIEW

Patient Input

TAFAMIDIS (TBC)

Pfizer Canada

Indication: Transthyretin-mediated amyloidosis

CADTH received patient input from:

Canadian Organization for Rare Disorders with support of Canadian Amyloidosis Support Network

July 25, 2019

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Tafamidis**
Name of the Patient Group	**Canadian Organization for Rare Disorders with support of Canadian Amyloidosis Support Network**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Canadian Organization For Rare Disorders (CORD)

CORD is Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research, diagnosis, treatment and services for all rare disorders in Canada.

https://www.raredisorders.ca/

The CASN is a not-for-profit, all volunteer organization, formed by amyloidosis patients and family members of amyloidosis patients. The CASN offers a toll-free helpline, an educational website, and a support community connected through social media and meetings.

http://thecasn.org/

2. Information Gathering

Recruitment: Participants were recruited through three sources: two patient networks for amyloidosis and individual clinicians treating patients with amyloidosis. The outreach was specific to those patients who were diagnosed with (or suspected of having) Transthyretin Amyloid Cardiomyopathy (ATTR-CM), either inherited or wild-type. Hereditary ATTR-CM is caused by a gene change (mutation) and generally runs in families and may be symptomatic at any age from post-adolescence to senior. Those with wild-type ATTR-CM do not have a gene mutation and symptoms generally start after age 65. Both networks are patient-based, offering education and support through website and Facebook as well as in-person meetings. The US-based network, Amyloidosis Support Groups, Inc. has support groups in over 35 US cities as well as global patient engagement, including the Canadian Amyloidosis Support Network, Inc. (CASN) based in Toronto (Canada). The CASN is a not-for-profit, all volunteer organization, formed by

amyloidosis patients and family members of amyloidosis patients. The CASN offers a toll-free helpline, an educational website, and a support community connected through social media and meetings.

There were two Canadian physicians who were taking part in tafamidis (expanded) clinical trials, and they agreed to approach patients to request permission to share their contact information so they could be interviewed for the patient submission process. Four patients were interviewed, all the same interviewer.

Responses: Patients provided input through individual interviews (4) and online survey (42). All those who provided individual interviews were asked to complete the online survey, but we do not know the actual overlap. The survey link was distributed to all members of the amyloidosis groups with instructions targeting patients and caregivers affected by ATTR-CM. For almost all of the questions, there were no significant differences between the Canadian and other respondents, so reporting will combine data from all, except where there are notable differences.

Among the 42 on-line respondents, 45% identified as a person diagnosed with wild-type ATTR-CM (wATTR-CM); 26% were diagnosed with hereditary ATTR-CM (hATTR-CM); another 5% had symptoms consistent with ATTR-CM but had no confirmed diagnosis. Another 2% (1 person) reported a very rare type of ATTR-CM that included both hereditary and wild-type, and 2% (I person) reported being unable to get a confirmatory diagnosis. Among respondents, 19% (8 persons) were caregivers.

Diagnosis: The respondents reflected the range of ATTR-CM patients. The majority (66%) were diagnosed when they were between the ages of 60 and 79 years old, while less than one-third (29%) were diagnosed between 40 and 59 years old. Less than 6% said they were between 20 and 39 years old when diagnosed and none were over the age of 80 when diagnosed.

In terms of time since diagnosis, about half (52%) said it had been diagnosed for two to five years. Almost one-fourth (24%) said they had been diagnosed for less than one year, while one-fifth (21%) said they had received their diagnosis between one and two years ago, and another 3% had been diagnosed about five to 10 years ago.

Demographic Information: The majority of the patients represented in the survey identified as males (87%) and 11% as females (with 2% not identified). Among those who specified a country of residence (38 respondents), 50% were in the USA, 45% in Canada, and 5% elsewhere (Australia). Among Canadian respondents, about 35% reside in Ontario; 29% in British Columbia, and 29% in Alberta (remaining unspecified).

3. Disease Experience

Interviewees and survey respondents were asked to describe in their own words the experience of living with or caring for someone with ATTR-CM, as well as the impact on family and others. Almost all patients (or caregivers) reported that the condition was debilitating, interfering significantly with daily functioning and quality of life. Like all types of ATTR, the condition affects multiple systems in the body. *ATTR-CM has limited the activities my husband is able to do such as walk any distance at all. He is unable to do the normal day to day functions. He is totally winded doing things such as getting dressed, tying up shoes, going up stairs etc. depending on family do to any necessary chores as changing light bulbs, any yard work, auto repairs, going to the store etc.*

The impact on me is significant: my capacity for exertion is approximately 50% of what it was; I was no longer able to retain a career that included a heavy travel schedule and long working hours; I experienced a forced retirement long before I was mentally ready or prepared to accept the necessary adjustments required when in retirement.

I was an airline captain, this diagnosis ended my career as I could no longer hold a medical for my license. Financially the impact has been huge ending my career 9 years early. I have been slowly losing the physical capacity to do almost all of the physical activities I did regularly to maintain a high level of fitness and recreation (endurance swimming, mountain biking, hiking). I am still able to golf and downhill ski but those activities will soon demand more fitness than I can muster.

The fear of living with a fatal disease, no real time frame, with no potential cure in site, is devastating to the whole family. Causes a rollercoaster of emotions for all.

constant fatigue creating a problem of carrying out the smallest task. … I find myself wanting to with draw from a situation because of a need to rest, this causes me to become withdrawn and depressed. … without the research program that supplies the medicine free it would/could be a great burden causing a lot of stress to myself and family.

it has affected my family in that I have a serious loss of energy. I am able to walk 10 to 20 steps at a time. The majority of my daily life chores is undertaken by family.

Financial - now down one income - trying to keep house afloat. Caregiver works two part-time jobs equaling way more than 60 hours per week. Always worried about low blood pressure causing patient to fall. Patient is alone much of the time. Daughter who is away in the army and trying to study for her skill is having trouble focusing...

After 3 years of in and out of hospitals defibrillator dubudomine IV pump several cardio ablations and episodes of Afib I had to get a heart and liver transplant A roller coaster ride ever since. My neuropathy and arthritis has gotten painfully worse I have osteoarthritis

The survey presented a list of physical effects of ATTR-CM and respondents were asked to rate the degree to which they experienced each, on a five-point scale identified as “no problem, never”, “minor, infrequent”, “moderate, sometimes”, “serious, frequent”, and “incapacitating, regularly.” While this form of ATTR has a major impact on the heart, the symptoms rated as most difficult were those related to “nerve damage: tingling, numbness, burning pain, carpel tunnel, weakness” with nearly three-fifths (59%) reporting the impact was “serious” or “incapacitating.” Only 14% reported no problems with neuropathy while the remaining 28% said the symptoms were “moderate.”

Second among symptoms were those related to cardiac functioning namely, shortness of breath, with more than one-fourth (28%) reporting these “serious” or “incapacitating”, while about three-fifths (59%) reported these were “moderate.” About one-fifth (22%) said symptoms of “swelling in feet, ankles, and legs” were “serious”, but about one-half (51%) said these were experienced “never” or “infrequently.” Other cardiac-related symptoms, specifically, “palpitations, arrhythmia, and chest pain” were “serious” for only one-fifth (21%), while nearly half (48%) said these were “never” or “infrequently” experienced.

Finally, impact on cognitive functioning (e.g., confusion, headaches, trouble thinking) was much less of an issue for most respondents, with about one-half to three-quarters reporting “no problem” or “never” experiencing these impacts.

4. Experiences With Currently Available Treatments

Specific treatments: benefits, side effects and management: Prior to tafamidis, there have been no therapies specific to ATTR-CM. Almost all patients (86%) did report receiving treatment to manage symptoms related to organ damage, namely heart damage, nerve damage, and inflammation. However, among Canadians, only 71% said they received previous treatment (not including tafamidis) while 29% had not

Survey respondents were presented with a list of treatments and asked to indicate whether they used in the past, were using currently, or had used, with an option for “not sure.” Given that the liver is the site of TTR production, liver transplantation was once considered a routine or “standardized” curative or life-extending option, albeit not recommended or accessible to all ATTR patients (given the lack of available livers for transplant). However, longer-term evidence indicated that symptoms often reoccurred, albeit with several intervening years of quality health.

Only two respondents indicated receipt of a liver transplant; one of them resided in Canada and the other was in the USA. The therapy reported as used by most respondents currently (two-thirds or 67%) either medicines to manage fluid and/or mineral levels (e.g., electrolytes, mineral and vitamin supplements), with 13% reporting previous use. About half (50% – 54%) were currently taking some form of cardiac management therapy, specifically to manage blood pressure (e.g., diuretics) or regulate heartbeat (e.g.,

amiodarone) or blood thinners (e.g., warfarin) to minimize clots, with about 8% - 25% taking one or more of these cardiac therapies in the past. Diflunisal, a nonsteroidal anti-inflammatory drug was currently being used by about one-third, with one-third having taken them in the past, and one-third reporting no usage. A small number reported taking anti-bacterial treatments, home therapies, including green tea extract, and other medicines to manage GI distress.

In terms of two treatments specific for hereditary ATTR (with neuropathy) but not ATTR-CM, four respondents (all American) reported they are currently taking Onpattro (patisiran), a small interfering RNA-based drug that suppresses ATTR production, and one respondent (Canadian) reporting current use of Tegsedi (inosteren), an antisense oligonucleotide (ASO) that leads to degradation of TTR.

In addition, three respondents (American) reported they were in a clinical trial using AG10, a small molecule designed to potently stabilize tetrameric transthyretin, or TTR.

Effectiveness: Respondents were asked to rate the effectiveness of each therapy in managing ATTR-CM symptoms, on a five-point scaled anchored by "not at all" to "very well." For the American patients reported that it was "not at all" effective. In terms of liver transplant, patients reported the outcomes were "not at all" or "somewhat" effective in managing symptoms.

Among those taking medication to manage their cardiac symptoms (e.g., diuretics, blood thinners), most (two-thirds or about 68%) reported that the therapies worked well or very well for keeping their cardiac symptoms under control, (namely, blood pressure, arrhythmia or blood clots). For most of the remainder, these therapies were "somewhat" effective, with only very few ((5%) reporting they were "not at all" effective. Respondents reported similar ratings for treatments to manage fluid levels (with 68% saying they worked "well" or "very well" and about one-fourth (26%) saying they were "moderately" effective. Treatments to address inflammation (mainly Diflunisal) were regarded less well, with two-thirds saying "moderate" or "poor", while only one-third felt they worked well.

Among patients using patisiran, there was an even split between those reporting it was working "well/very well" and those who felt it worked "somewhat/poorly/not at all." For the patient on inosteren, the response was "unsure" at this time.

5. Improved Outcomes

Respondents were mostly pessimistic about the effectiveness of current treatment options. They were presented with an "open-ended" question, "Not including tafamidis (Vyndamax and Vyndaqel), how effective are the available treatments for ATTR-CM? Respondents were mostly pessimistic. Most indicated that they felt their therapies had little or no effect on in slowing or stopping disease progression.

Unknown. It's been difficult to diagnose the rate of progression of the wild-type ATTR cardiac amyloidosis, or to get any real sense of the prognosis of this disease for me.

They are somewhat ineffective.

Prior to being started on the Open Label Drug Trial for Tafamidis, I was given doxycycline and Ursodiol. I suffered very few side effects from that but seemed to need more BP control measures and more periodic use of diuretics.

They appear to maintain in a stable condition.

As far as we know there isn't any other effective treatment.

6. Experience With Drug Under Review

The survey was directed to all Canadian ATTR-CM patients and through the (USA) Amyloidosis Support Group to ATTR-CM patients, specifically those who have had experience with tafamidis (brand names Vyndamax and Vyndaqel). Overall, about two-thirds (67%) of respondents reported knowing about Onpattro and how it was used; with half of these saying they knew a lot about the medication. Only a small percentage (10%) said they were unaware of the drug while a similar number (13%) indicated they had heard of the drug but were not fully aware of its use. Awareness and knowledge were about the

same for the Canadian and American respondents. The high level of Canadian awareness reflects the fact that patients on clinical trials were directed to the interviews and surveys. This is reflected in the finding that half of those respondents who had experience with tafamidis were Canadians, with access through (expanded) clinical trials.

Comparison to others: benefits and disadvantages and impact on patients and family: Among all respondents, about 39% had received tafamidis and 61% had not; however, among Canadian respondents, 47% were receiving tafamidis and 51% were not. This reflects the deliberate recruitment through the Canadian clinicians of patients on clinical trials.

Respondents were asked to tell us, in their own words about the benefits of tafamidis, based on their experience and/or knowledge. The responses reflected both optimism and realism. There were two types of benefits that were consistently raised. The first referenced the impact on symptoms, namely reduction in nerve pain, increase in strength and energy, better appetite, and improved mobility. The second related but distinct benefit was "slowing or halting" disease progression. Thus, in their day-to-day life, patients felt better and were able to do more. As importantly, they were optimistic that this insidious disease was being held in check, if not actually cured.

I expect this drug to dramatically slow or perhaps even halt the progression of my disease. This would be wonderful - as I still have a quality of life worth living for. My diagnosis was early - due to the medical investigations required by my profession. I have recently started the 3rd stage clinical trial of Tafamidis. I have not experienced any adverse side effects after 6 weeks on the trial - and I hope to be able to claw back some of my previous fitness eventually.

I feel that it binds the miss folded [sic] TTR protein so it won't float around you blood settling on nerves & Organs, Hopefully this with stop the hardening of the left side of the heart.

My expectation for Tafamidis is that it will not cure or reverse the amyloid but will slow down the progression of the on going condition of the amyloid… At my age and condition I hope that it will provide me with at least the level of life style I currently have and will in the future help other people to live a good life in spite of the health problems.

I expect it to slow the progression of the disease, and I believe it has. Mortality, esp. for someone with long, undiagnosed, history is high. So I'm grateful that (I think) it's keeping me alive.

I have heard that it is about 40% effective, so should reduce the amount of amyloid deposit happening. It does not, however, remove amyloid that has already been deposited. This, it isn't a cure, but a way to delay or slow down the damage, hopefully buying the patient a better quality of life for a longer period of time.

Since starting Tafamidis 61 mg daily, [February 2019] I seem to require fewer diuretics [less lower leg edema] and my BP is more stable [home checks]. I have tested my exercise tolerance on a fixed number of stair steps [56] and over the past 6 months I complete that in the same amount of time.

Tafamidis, we hope will stabilize the deposits of amyloid fibrils, in the hopes of preventing further deterioration and perhaps offer an improvement in quality of life.

Almost all of participants receiving tafamidis reported they had experienced no side effects with the therapy (thus far). However, most say they have only been on therapy for a short time so also cannot really attest to the positive effects.

In my experience [6 months on Tafamidis 61 mg/ day] I have felt NO side effects.

I feel stable in terms of exercise tolerance. However I have had no follow up studies to compare left ventricular ejection fraction since starting.

No side effects to date...I have been on the drug for 6 months...61mg capsule, once per day.

7. Anything Else?

When asked about the importance of tafamidis to persons with ATTR-CM (hereditary or wild-type), they were unanimous in calling for availability to everyone, regardless of their current disease status.

I can't stress enough about having access to a therapy such as tafamidis. Any chance to maintain and perhaps improve one's ability to function in a productive manner is critical. Having an opportunity to lengthen one's lifespan is obviously invaluable. I have many things left to accomplish and would like to dance at my children's weddings and see my grand kids. These are my thoughts representing personal feelings on what the therapy may accomplish. However, I cannot believe that other families dealing with this disease are any different.

For a young family it would mean that a father or mother could continue to work to provide for the family, it would ease the burden of possible home care for the affected patient. I feel that without the medication a young family might suffer from a feeling of support in their lives for sports and personnel growth. I'm lucky as my amyloid is not hereditary and can only imagine how awful it would be to know that any of your children could be affected by the disease.

We would have [redacted] *for longer, maybe even time for a cue [sic]. We live in hope.*
Patients with ATTR amyloidosis with cardiac involvement have had no hope until recently.

This had been like a death sentence over the last several years. Now we have the possibility of a treatment, to perhaps stabilize and improve quality of life. It is imperative that this is approved and that these patients are given back some quality. It's been a long road.

…this drug offers hope where my understanding is that previously there was no known treatment for the disease. Although hard to quantify, hope encourages the pursuit of emotional, mental and physical health, all of which keep people out of hospitals.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No, the survey and analysis were conducted by the Canadian Organization for Rare Disorders

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No, we have no recollection of anyone entering the role.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Pfizer			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Durhane Wong-Rieger
Position: President & CEO
Patient Group: Canadian Organization for Rare Disorders
Date: 20 July 2019